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Overview on: Transdermal Drug Delivery System

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ABSTRACT

The transdermal drug delivery system is a technique that provides drug absorption via the skin. The system has many advantages over conventional administration routes such as intravenous or oral administration for systemic and local drug delivery with simple administration. It is available outside medical institutions, which decreases the burden on patients caused by intravenous administration and decreases loss from the first pass effect of the liver, delivering therapeutic drugs at a controlled ratio. Overcoming the skin barrier, including the stratum corneum and epidermal layer, is necessary to develop transdermal drug formulations. Although chemical and physical enhancers have been developed, they need high doses or high potency to exert efficiency, which induces irritation, causes damage, and reduces the skin barrier function.

KEYWORDS: *Drug Polymer matrix, Permeation enhancers, Backing membrane, Release liner, excipients*

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1. INTRODUCTION

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with motion sickness .[1]

TDD is a painless way of systemically administering medications by putting a drug formulation on unbroken and healthy skin. The drug goes through the stratum corneum first, then into the deeper epidermis and dermis, without accumulating in the dermal layer. The medication is available for systemic absorption once it reaches the dermal layer. It can be used as a non-invasive alternative to parenteral methods, avoiding injection fear. The extremely large surface area of skin and ease of access allows for a variety of transdermal absorption, placement choices. Furthermore, medication pharmacokinetic profiles are more consistent and have fewer peaks, reducing the possibility of severe side effects. It can enhance patient compliance by lowering dose frequencies and is also appropriate for patients who are unconscious or vomiting, as well as those who self-administer. Several dosages, insufficient drug delivery, or characteristics of diverse medications typically result in low therapeuticbenefits; therefore transdermal drug delivery has piqued the interest of researchers with multiple proposals.[2]

Advantages of TDSS [3]

Transdermal delivery route is convenient and safe and hence it is one of the preferred method to deliver drugs across the skin to get the systemic effects which are given below

1. Avoidance of 'first-pass' metabolism of drugs.
2. Reduced plasma concentration levels with decreased side effects.
3. Reduction of fluctuations in plasma levels.
4. Utilization of drug candidates with short half-life and low therapeutic index.
5. Reduction of dosing frequency and enhancement of patient compliance.
6. Improving physiological and pharmacological

response.
7. Avoiding the fluctuation in drug level.
8. Maintain plasma concentration of potent drugs.
9. Termination of therapy is easy at any point of time.
10. Ability to deliver drug more selectively to a specific site.
11. Provide suitability for self-administration;
12. Enhance therapeutic efficacy
13. Drugs that are highly melting can be given by this route due to their low solubility both in water and fat.

Limitations of TDDS [4]

All types of drugs can't be administered through this route; the drug must have some desirable Physico-Chemical properties.

1. Not suitable for drugs that require high plasma levels.
2. Not suitable for drugs that produce skin irritation and contact dermatitis.
3. Not suitable for drugs with high molecular weight.
4. Not suitable for drugs that undergo metabolism during the passage through the skin.
5. The Transdermal route cannot be employed for a large number of drugs, as the skin is a very efficient barrier for penetration of drugs.
6. Only with low dose can be administered
7. The barrier nature of the skin changes from one site to another in the same person, fromperson to person and also with age.

Applications of TDDS [5]

1. To promote adequate drug delivery, hisetal, which is used to treat multiple sclerosis, can be synthesized in TDDS with oleic acid as a permeability enhancer.
2. Non -steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium and celecoxib may be formulated in TDDS to avoid the stomach lesions associated with oral dosage.
3. Drugs with a short biological half and significant first pass metabolism, such as captopril, verapamil, terbutaline sulphate, pinacidil, and propranolol, that are used for long term dosage in chronic conditions, can be manufacture as TDDS to obtain prolonged steady state plasma concentration
4. Drug release may be accelerate using hydrophilic polymers like polyvinyl pyrrolidone, while drug delivery may be delayed with hydrophobic polymers like ethyl cellulose.
5. The use of a gel formulation with a betahistine lipid dispersion system could lead to the creation of an effective controlled release transdermal system.

2. BASIC COMPONENETS OF TRANSDERMAL DRUG DELIVERY SYSTEMS [4]

The components of Transdermal device include-

1. Drug.
2. Polymer matrix.
3. Permeation enhancers.
4. Backing membrane.
5. Release liner
6. Other excipients

1. Drug:

For successfully developing a Transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for Transdermal delivery.

- Physicochemical Properties:

a) The drug should have a molecular weight less than approximately 1000 Daltons.
b) The drug should have affinity for both- lipophilic and hydrophilic phases.
c) Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
d) The drug should have a low melting point.

- Biological Properties:

a) The drug should be potent with a daily dose of the order of a few mg/day.
b) The half-life (t1/2) of the drug should be short.
c) The drug must not induce a cutaneous irritation or allergic response.
d) Tolerance to the drug must not develop under the near zero-order release profile of Transdermal delivery.

Drugs, which have to be administered for a long period of time or which cause adverse effectsto non-target tissues can also, be formulated for Transdermal delivery.

2. Polymer Matrix:

Polymer matrix, prepared by the dispersion of a drug in a suitable polymer, controls the release of thedrug from the device. Polymers used in TDDS should be stable, compatible and nonreactive with the drug and other components of the system, should provide effective release of the drug throughout the device. They should be easily fabricated to the desired product. Polymers and their degradation products must be non-toxic and non- antigenic to the host. The polymers used for TDDS can be classified as:

Natural Polymers	Synthetic Elastomers	Synthetic Polymers
Cellulose derivatives,Zein, Gelatin, Waxes,Proteins, Gums, Natural rubber, Starch	Polybutadiene, Hydrin rubber, polysiloxane, siliconerubber, Nitrile, Acrylonitrile,Butylrubber, Styrenebutadiene, Neoprene etc.	Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyvinylpyrrolidone, Polymethyl methacrylate, Epoxy, Polyurea, etc.

(Table No.1: different types of polymers)

3. Permeation Enhancers:

Chemical permeation enhancers:

They disrupt the highly ordered intercellular lipid bilayers of the stratum corneum by inserting amphiphilic molecules or by extracting lipids, reversibly decreasing the barrier resistance and allowing better permeation of the co-administered drugs. An ideal enhancer should be inert, non- toxic, non-allergenic, non-irritating, work unidirectionally and compatible with the excipients and drugs. Their potency appears to be drug, skin and concentration dependent.

examples –

ethanol (the most common permeation enhancer), essential oils or terpenes (cineole, carveol, menthone, citral, menthol, dimethyl sulfoxide sodium lauryl sulfate, pluronic, oleic acid, urea,	propylene glycol, N-methyl-2-pyrrolidine,ethyl pyrrolidine, polyethylene glycol 400, isopropyl myristate, myristic acid, succinic acid, methyl laureate, lauric acid,, non-ionic surfactant (spans, tweens)

Physical permeation enhancers:

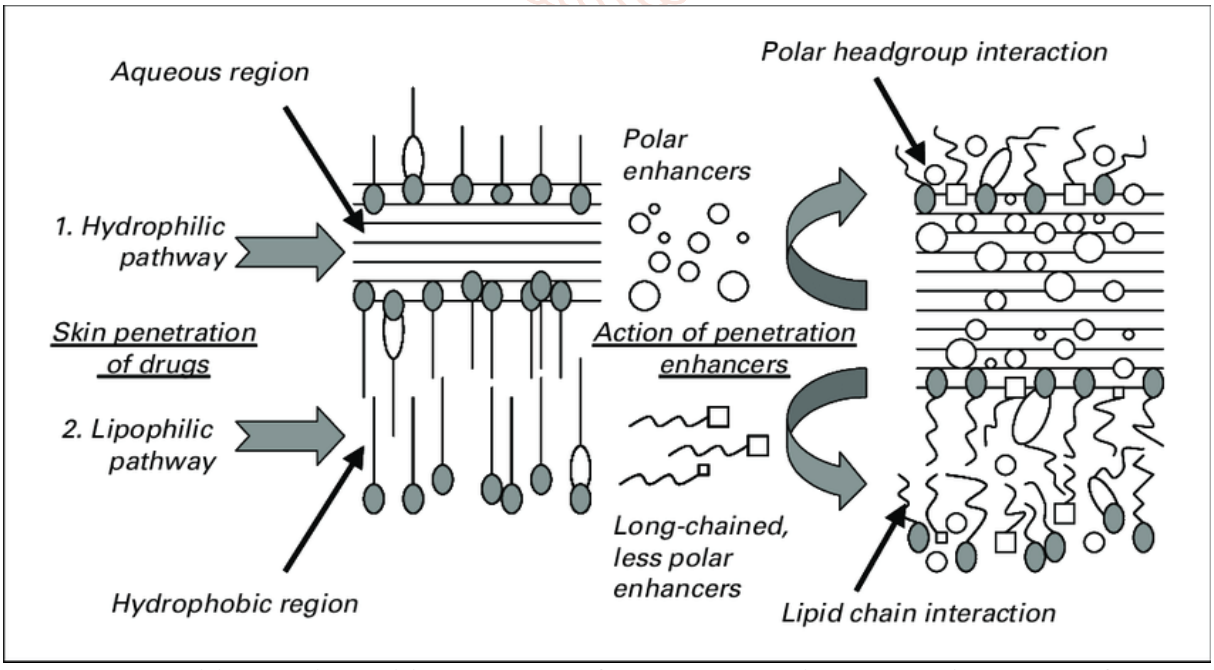
Iontophoresis enhance and control drug penetration through the skin by applying low density electric cur-rent. Electroporation applies high voltage pulses across the skin for a fraction of second, creating new aqueous pathways in the stratum corneum for drug diffusion. Erbium: yttrium-aluminium-garnet laser applies single pulse of low energy to ab-late the stratum corneum layers.Ul-trasound or micro needle application breach the stratum corneum and create micro channels for the drug permeation.

Other permeation enhancers:

Ethanolic liposomes, niosomes, protransferosome gel and prodrug approach are reported to increase permeability by increasing the drug solubilization and partitioning into the skin

- **Mechanism of penetration enhancers:**

penetration enhancers which penetrate into skin to reversibly decrease the barrier resistance. Many potential sites and modes of action have been identified for skin penetration enhancers; the intercellular lipid matrix in which the accelerants may disrupt the packing motif, the intracellular keratin domains or through increasing drug partitioning into the tissue by acting as a solvent for the permeant within the membrane. Further potential mechanisms of action.



(Figure1: Hydrophilic and lipophilic pathways of drug penetration and action mode of penetration enhancers)

4. Backing Membrane:

Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear, pigmented, or metallized form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission ratesto promote increased skin hydration and, thus, greater skin permeability.

Examples:

vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin,Polyurethylene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate.

5. Release Liner:

Release liner is a protective liner for the TDDS patch that is removed prior to the application on the skin. Typically, it consists of a base layer which may be-

1. non-occlusive (e.g. paper fabric)
2. occlusive (e.g. polyethylene, polyvinylchloride)

During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foiland metalized laminate

6. Other excipients:

A. Solvents:

These compounds increase penetration possibly by

1. Swelling the polar pathways in the skin.
2. Fluidization of lipids.

Examples:

water alcohols-methanol and ethanol; alkyl methyl sulfoxides-dimethyl sulfoxide, alkyl homologs of methyl sulfoxide, dimethyl acetamide and dimethyl formamide; pyrrolidones-2- pyrrolidone; laurocapram (Azone), miscellaneous solvents-propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

B. Surfactants:

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the head group and the hydrocarbon chain length. These compounds are skin irritants, therefore, a balance between penetration enhancement and irritation have to be considered. Anionic surfactants can penetrate and interact strongly with the skin. Once these surfactants have penetrated the skin, they can induce large alterations. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the three major classes of surfactants, the nonionic have long been recognized as those with the least potential for irritation and have been widely studied.

Examples of commonly used surfactants are:

- Anionic Surfactants: Dioctyl sulphosuccinate, Sodium lauryl sulphate,Decodecylmethylsulphoxide etc.
- Nonionic Surfactants: Pluronic F127, Pluronic F68, etc
- Bile Salts : Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

C. Miscellaneous Chemicals:

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-mtoluamide; Calcium thioglycolate; Anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness are sparse. These include eucalyptol, di-o-methyl-betacyclodextrin and soyabean casein.

D. Adhesives:

The fastening of transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally.

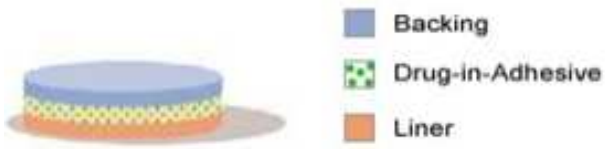
Both adhesive systems should fulfill the following criteria-

a) Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora.

b) Should adhere to the skin aggressively during the dosing interval without its positionbeing disturbed by activities such as bathing, exercise etc.
c) Should be easily removed.
d) Should not leave an unwashable residue on the skin.
e) Should have excellent (intimate) contact with the skin at macroscopic andmicroscopic level.

Types of Transdermal Patches: [7]
There are four Major Transdermal Systems

Single-layer Drug-in-Adhesive
The Single-layer Drug-in-Adhesive system is characterized by the inclusion ofthe drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin .

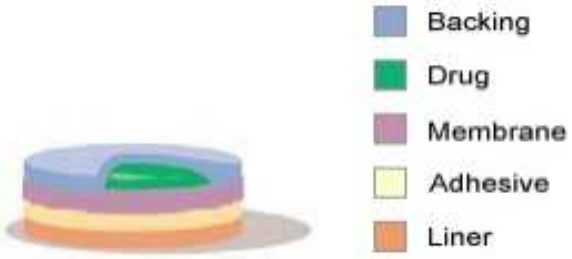


(Figure 2.: Single-layer Drug-in-Adhesive)

Multi-layer Drug-in-Adhesive:
The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition ofa membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in- adhesive layers under a single backing film.

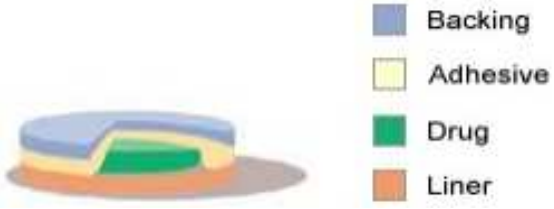
(Figure 3.: Multi-layer Drug-in-Adhesive)

Drug Reservoir-in-Adhesive:
The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.



(Figure 4: Drug Reservoir-in-Adhesive)

Drug Matrix-in-Adhesive:
The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.



(Figure 5: Drug Matrix-in-Adhesive)

3. METHODS FOR PREPARATION OF TRANSDERMAL PATCHES: [4]

Transdermal drug delivery patches can be prepared by various methods.

A. Mercury Substrate Method:

In this method required amount of drug is dissolved in predetermined amount of polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is keep aside until air bobbles removed completely and then poured in to a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The dried films are to be stored in a desiccators.

B. Circular Teflon Mould Method:

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Plasticizer added into drug polymer solution. The total contents are to be stirred and then poured into a circular teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in a desiccators.

C. Glass Substrate Method:

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and dry anumbra petriplate. The rate of solvent evaporation is controlled by inverting a glass funnel over the petriplate. After overnight, the dried films are taken out and stored in a desiccators.

D. By Using IPM Membranes Method:

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanol amine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

E. By Using EVAC Membranes Method:

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device .

F. Aluminium Backed Adhesive Film Method:

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks.

G. Asymmetric TPX Membrane Method:

A prototype patch can be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

4. EVALUATION PARAMETERS[8]

The various evaluation parameters of TDDS are discussed below:

A. Interaction Studies

The stability of a formulation amongst other factors depends on the compatibility of the drug with theexcipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used informulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

B. Thickness of the Patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

C. Weight Uniformity

The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

D. Folding Endurance

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

E. Percentage Moisture Content

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.

F. Percentage Moisture

Uptake Films are weighed and kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs, the films are reweighed and the percentage moisture uptake is determined from the below mentioned formula.

Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100.

G. Water vapour permeability (WVP)

evaluation Water vapour permeability is usually determined with foam dressing method. The air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula:

WVP=W/A

where, WVP is expressed in gm/m^2 per 24hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs A is the surface area of the exposure samples expressed in m^2 .

H. Drug Content

A specified area of patch is dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

I. Uniformity of Dosage Unit Test

An accurately weighed portion of the patch is cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution is allowed to settle for about an hour, and the supernatant is suitably diluted to give the

desired concentration with suitable solvent. The solution is filtered using 0.2m membrane filter and analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece is calculated.

J. Polariscope Examination

This test is performed to examine the drug crystals from patch by polariscope. A specific surface areaof the piece is kept on the object slide and observed for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

K. Shear Adhesion Test

This test is performed for the measurement of the cohesive strength of an adhesive polymer which is influenced by the molecular weight, the degree of cross linking and the composition of polymer, typeand the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

L. Peel Adhesion Test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular wt of the adhesive polymer, the type and amount of additives, and polymer composition. Itis tested by measuring the force required to pull a single coated tape, applied to a substrate, at an1800 angle. No residue on the substrate indicates 'adhesive failure' which is desirable for transdermal devices. Remnants on the substrate indicate 'cohesive failure' signifying a deficit of cohesive strength in the coating.

M. Thumb Tack Test

This test is for tack property determination of adhesives. The thumb is simply pressed on the adhesive and the relative tack property is detected.

N. Flatness Test

Three longitudinal strips are cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

O. Percentage Elongation Break Test

The percentage elongation break is determined by noting the length just before the reak point, thepercentage elongation can be determined from the below mentioned formula.

Elongation percentage = L_1-L_2 ×100 L_2.Where, $L_1$is the final length of each strip

L_2 is the initial length of each strip.

P. Rolling Ball Tack Test

This test measures the softness of a polymer. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

Q. Quick Stick (Peel-tack) Test

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

R. Probe Tack Test

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams

S. In vitro drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

T. In Vitro Skin Permeation Studies

In vitro permeation study is carried out by using diffusion cell on full thickness abdominal skin of male Wistar rats of weights 200 to 250g. Hair from the abdominal region is removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant.

The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is replaced. Samples are filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm2) vs. time in hours and permeability coefficients is deducedby dividing the flux by the initial drug load (mg cm2).

U. Skin Irritation study

Skin irritation and sensitization testing is performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is cleaned and the hairs are removed from the clean dorsal surface by shaving and cleaning the surface by using rectified spirit and the representative formulations is applied over the skin. The patch is removed after 24 hr and the skin is observed and classified into 5 grades on the basis of the severity of skin injury.

V. Stability studies

Stability studies are conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0,30,60,90 and180 days. Drug content is analyzed.

5. Formulation of transdermal patch [9]

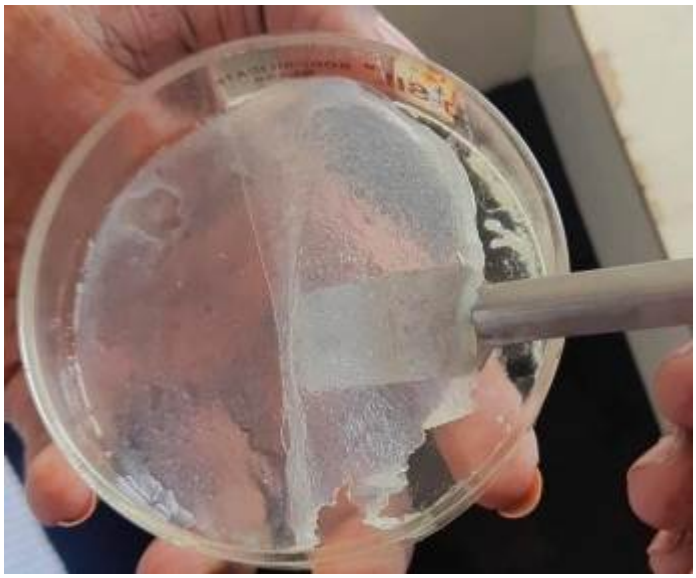
The transdermal patch was prepared by solvent casting technique employing mercury as a substrate using glass petri plate. The polymer hydroxyl propyl methyl cellulose E5 and xanthan gum were used with different concentration. The polymers were accurately weighed and dissolved in 10 ml of distilled water and methanol in the ratio of (8:2) solvent. The solution was then kept on magnetic stirrer and adequate amount of penetration enhancers were added in each batch in beaker containing polymeric solution. linseed oil was used as penetration enhancer with different concentration in all formulations. The polymeric solution was kept on magnetic stirrer for 2 hrs at the rate of 100 rpm.PEG-400 used as plasticizer so as to stop the breakdown of patch. After stirring the solution it was poured in the petri plate. Then the solution kept in hot air oven for 3-4 hrs at temp 30- 400C for drying the patch and it was then easily removed from the petri plate.

Table 2: Composition of Transdermal Patches

Ingredients	F3	F6	F9	F12
Xanthan gum(mg)	100	150	-	-
HPMC E5(mg)	-	-	300	400
PEG-400(%)	15	15	15	15
Linseed oil(%)	2	4	2	4
Methanol(ml)	2	2	2	2
DW(ml)	8	8	8	8

6. RESULT-

The transdermal patches were prepared using various polymers such as HPMC E5 and xanthan gum. The prepared formulations transdermal patches were found to be clear, transparent and smooth.



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